REVIEW ARTICLE

POLYMORPHISM IN PHARMACY

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A. INTRODUCTION

Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystalline species eg. carbon as a cubic diamond or hexagonal graphite.[1] A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of the compound in the solid state. The molecule itself may be of different shape in the two polymorphs but that is not necessary and indeed, certain changes in shape involve formation of different molecules and hence do not constitute polymorphism. Geometric isomers or tautomers, even though interconvertible and reversibly so, cannot be called polymorphs, although they may behave in a confusingly similar manner.[2]

The fact that a compound can exist in a crystalline form does not mean that it will always crystallize in one particular crystal system. If a compound can exist in two (or more) forms, these are denoted polymorphs. When polymorphism exists, the molecules can arrange themselves in two (or more) different ways in crystalline state. The molecules in the two forms are chemically identical. Certain shape changes of a molecule in the two forms may occur, but these are not what are known as 'Chemical Changes'. Such non chemical changes encompass resonance structures, rotations about single bonds, and slight bond-distance alterations. A good criterion for distinguishing between polymorphs and chemically different entities is that in the former case the two crystal phases form chemically identical melts and vapours. The composition of saturated solutions and their vapour pressure, however will be different for the two polymorphs and this is of pharmaceutical importance.

The form isolated at any given time may be influenced by the nature of the crystallizing solvent (s) as well as the process or parameters of crystallization. A classical example of polymorphism found in nature, which highlights the physical and chemical differences that can exist between polymorphs is that observed between hexagonal carbon graphite and cubic diamond.[4]

The polymorphs show different solubilities and rates of solution, hence different absorption (bioavailability) tendencies. Thus, polymorphic transformations are structural differences resulting from different arrangements of molecules in the solid state. Polymorphism as it pertains to physical and chemical stability and also to the therapeutic activity has been discussed by a number of researchers.[5]

Different polymorphs of a given compound are in general as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapour pressure, stability, etc. all vary with the polymorphic forms. In general, it should be possible to obtain different crystal forms of a drug substance and thus modify the performance properties for that compound. To do so requires a knowledge of the behaviour of polymorphs. There are numerous reviews on the subject of polymorphism. In addition, numerous indications of the

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importance of polymorphism in pharmaceuticals are reported in the literature. The work of Kubnert — Brandstatter et al with steroids, barbiturates, and antihistamines probably represents the most intensive study of polymorphism and drugs.[8] They emphasized that almost one in every three compounds exhibit polymorphic behaviour. When the change from one polymorphic form is reversible it is said to be enantiotropic but when the transition takes place in one direction only i.e. from a metastable form to a stable form it is said to be monotropic. Polymorphism is known to occur in many steroids, in sulphonamides and barbiturates, the occurance being frequent in complex molecules, particularly if hydrogen bond formation is possible within the molecules. When a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra in solution. Sulphathiazole exists in at least two polymorphic forms, one of which (Form I) undergoes a change in crystal structure at about 174° to form II that melts at 180°. Form I can be prepared by crystallization of sulphathiazole from boiling water or 95% ethanol and seems to be the form commonly met in practice. Cortisone acetate exists in several crystalline forms, only one of which is suitable for preparing stable aqueous suspensions. The unstable forms undergo a polymorphic change in the pressence of water which results in crystal growth. The biological activity of chloramphenicol palmitate has been correlated with polymorphic behaviour.[7]

Four different polymorphic forms of oil of theobroma have different melting points. Heating it to 38° completely liquifies the fat but destroys the beta stable crystal (melting point 34.5°) the crystal that are formed being the meta stable, gamma, alpha and beta forms melting at 18°, 22° and 28° respectively so that suppositories tend to melt at room temperature. By melting the oil of theobroma at the lowest possible temperature (about 33°) the stable beta form is not lost and a suppository stable at room temperature is produced. Hydrogenated vegetable oils are also used as suppository bases but as they are unlikely to exist in polymorphic forms they are not affected by slight overheating.

A safe criterion for classification of a system as polymorphic is the following. The polymorphs will be different in crystal structure but identical in the liquid or vapour states. Dynamic isomers will melt at different temperatures, as do polymorphs, but will give melts of different composition. In time, each of these melts changes to an equilibrium mixture of the two isomers with temperature dependent compositions. Some reported cases of polymorphism are undoubtedly dynamic isomerism since the two behave quite similarly.[9]

Methods for obtaining Polymorphs.[10]

The initial task of the performulator is to determine whether or not the drug substance being evaluated exists in more than one crystalline form. The following procedures are usually followed to cause crystallization of a metastable form.[11]

(a) Melt completely a small amount of the compound on a slide and observe the solidification between crossed polars. If after spontaneous freezing, a transformation occurs spontaneously or can be induced by seeding or scratching, the compound probably exists in at least two polymorphic forms. It is essential to prevent nucleation of the stable form by inducing supercooling. Supercooling can be induced by using a small sample size by holding the melt for approximately 30 seconds about 10° above the melting point, by carefully setting aside the compound without physical shock before observing it, and by rapid cooling of the compound.

(b) Heat a sample of the compound on a hot stage and observe whether a solid-solid transformation occurs during heating.

(c) Sublime a small amount of the compound and attempt to induce a transformation between the sublimate and the original sample by mixing the two in a drop of saturated solution of one of them. If the two are polymorphs, the more stable one will be more insoluble and will grow at the expense of the more

soluble metastable form. This process will continue until the metastable form is completely transformed to the stable form. If the samples are not polymorphs, one may disolve but the other will not grow. If the two are identical forms nothing will occur.

(d) Maintain an excess of the compound in a small amount of solvent held near the melting point of the compound. Isolate the suspended solid. Care should be taken to maintain the temperature during this step. Test the isolated material with an original sample using the procedure outlined in (e).

(c) Recrystallize the compound from solution by shock cooling and observe a portion of the precipitated material suspended in a drop of the mother liquor. The drop may then be seeded with the original compound to check for solution biphase transformation. If the precipitate is a different polymorph, a solution phase transformation should take place. Once it has been established that polymorphism occurs there are procedures which enable the preformulator to prepare the various forms in larger quantities for further evaluation and suitability for incorporation into dosage forms.

Methods of Identification of Polymorphs

Once a compound has been shown to exist in more than one crystalline form, a number of techniques are available to identify the different polymorphic phases present. Each of these techniques could be successful in identifying the phase, but a combination of methods provides a means for isolation, and identification of each crystalline modification. In order to confirm the pressence of more than one crystalline form of a compound it is advisable to identify the modifications present by more than one method. Using only one method for confirming the presence of polymorphs may sometimes be misleading.

i) Microscopy : Optical crystallography is used in the identification of polymorphs. Crystals exist in isotropic and anisotropic forms. When isotropic crystals are present the velocity of light is the same in all directions. While ansotropic crystals have two or three different light velocities or refractive indices. This method requires the services of a trained crystallographer.

ii) Hot Stage Methods : The polarizing microscope fitted with a hot or cold stage is very useful for investigating polymorphs. An experienced microscopist can quickly tell whether polymorphs exist, the degree of stability of the metastable forms, transition temperatures, and melting point, rates of transition under various thermal and physical conditions and whether to pursue polymorphism as a route to improved dosage form. Kodlers and Mc Crone discuss these methods in detail.

iii) X-Ray Powder Diffraction : Crystalline materials in powder form give characteristic x-ray diffraction patterns made up of peaks in certain positions and varying intensities. Each powder pattern of the crystal lattice is characteristic for a given polymorph. This method has the advantage over other identification techniques in that the sample is examined as presented. Some care should be exercised in reducing and maintaining particle size control. A very small sample size is needed and the method is non destructive. This method has been used by several investigators in identifying polymorphs in pharmaceuticals.

iv) Infrared spectroscopy : This procedure is useful in identification of polymorphs. Solid samples must be used since polymorphs of a compound have identical spectra in solution. The technique can be used for both qualitative and quantitative identification.

v) Thermal Methods : Differential scanning calorimetry and differential thermal analysis have been used extensively to identify polymorphs. In both methods the heat loss or gain resulting from physical or chemical changes occuring in sample is recorded as a function of temperature as the substance is heated at a uniform rate. Enthalpic changes both endothermic and exothermic are caused by phase transitions. For example fusion, sublimation, solid-solid transition, and water loss generally produce endothermic effects while crystallization produces exothermic effects. Thermal analysis enables one to calculate the thermodynamic parameters for the system being evaluated. Guillory obtained the heats of fusion for sulfathiazole and methyl prednisolone. Ravin et al utilized differential scanning calorimetry to follow the rate of conversion of sulfathiazole polymorphs.

vi), Dilatometry : Dilatometry measures the change in volume caused by thermal or chemical effects. Ravin & Higuchi,[13] utilized dilatometry to follow the melting behaviour of theobroma oil by measuring the specific volume of both rapidly and slowly cooled, theobrome oil as a function of increasing temperature. The presence of the metastable form was shown by a contraction in the temperature range 20° to 24° C. Dilatometry is extremely accurate, however, it is extremely tedious, and time consuming. It is not widely used.

Proton magnetic resonance, nuclear magnetic resonance and electron microscopy are sometimes used to study polymorphism.[13]

vii) Laser Raman Spectroscopy : Bellows, Chen, and Prasan,[14] determined drug polymorphs by means of the Laser Raman spectroscopy. This Raman Spectroscopy of the lattice vibrations (Phonon) was used to distinguish among various forms of ampicillin (I) and griseofulvin (II). The two anhydrous polymorphs of I and the trihydrate were identified. II solvates with benzene and chloroform were differentiated and the spectra suggested that the II lattice structure expanded to accept chloroform, but that the benzene solvates had a different crystal structures.

I. **Preformulation :**

Lachman, Swartz, and Huebner in their paper reported (a) the physical and chemical characteristics especially the dissolution properties of three salt forms of 1-(2,3, dihydro-5 methoxy benzo (b) furan -2-yl methyl) -4- (o methoxy phenyl) piperazine (I), a potential antihypertensive compound and (b) the relationship between the salt form and biological activity in dogs.

The dissolution kinetics and thermodynamic parameters of polymorphs of I are considered in part II, of their paper.[15]

II. **Biopharmaceutics**

A. **Kinetics**

Shami et al used the differential scanning calorimetry for the determination of sulfathiazole form I in the presence of sulfathiazole form II. An activation energy of 56 kcal/mole was calculated for the system.[16]

The effect of various additives on the rate of transformation of the metastable anhydrous succinyl sulfathiazole (I) form I to the water soluble dihydrate form II in aqueous suspensions was studied by Ebain, Moustafa, and Khalil.[17]

Some structurally related compounds, viscosity imparting agents, surfactants, and colouring agents were used as possible transformation retardants. The effect of including seeds of Form II in the presence and absence of additives was also discussed. Some additives eg. methyl cellulose and pthalylsulfathiazoles showed significant transformation retarding effects. Other additives eg. sulfanilamide and glycerin increased the rate of transformation.

Colouring agents had only slight effects. Utilization of the results in the formulation of physically stable aqueous suspensions of I was discussed.

Using differential scanning calorimetry and thermomicroscopy, Echert and Muller studied the formation and transformation with time of the different polymorphic modifications obtained during the crystallization of I-(5-oxohexyl)-theobromine in vitreous supercooled melts.[18]

B. Dissolution

Andersgaard and Finholt determined the dissolution rates of chloramphenicol palmitate polymorph A and B in phosphate buffer pH. 7.5, containing 0.05% polysorbate 80. This was then compared to the rates of the enzymatic hydrolysis of the two polymorphs by pancreatin in the same phosphate buffer.

The rate of hydrolysis, especially of polymorph B. was so high compared to the rate of dissolution that the first step of the enzymatic process cannot be a dissolution of the ester. It was more likely that chloramphenicol was attached in undissolved state by an enzyme from the pancreas, probably the pancreatic lipase.[19]

Then Frokjaer and Andersen, proposed a model to aid the analysis of the dissolution phenomens occuring with polymorphism in metastable drugs.

The model was tested experimentally by a rotating disk method using testosterone which changes to testosterone monohydrate II in water. It was possible to determine the solubility of testosterone. The rate constants of the transport process and the crystallization process were also estimated. The dissolution process for testosterone and the monohydrate was found to be transport controlled. From the solubilities at various temperatures of the 3 modifications (1 anhydrate and 2 mono-hydrates) the enthalpy changes and the equillibrium temperatures associated with their phase interconversions were determined. The results agree with those from thermoanalytical investigations of the system.[20]

Niazi, found that the dissolution rates of the 2 polymorphic forms of sulfathiazole containing polyethylene glycol 4000(1) were significantly different in water. At higher stirring speeds the dissolution rates in water. At higher stirring speeds the dissolution rates of the stable forms were effected more than the stable form. A high concentration of I seemed to affect the dissolution properties of the metastable polymorph more than the stable polymorph.[21]

Similarly Corrigan, and Timoney found the incorporation of hydroflumethiazide (I) with polyvinyl pyrrolidone (Povidone II), to retard and to enhance the dissolution of the drug from compressed disease, the magnitude of the effect being dependent on the proportion of II present and its method of in corporation.

The most active system dissolved 16 times faster than pure I. Low concentrations of II were also found to decrease the apparent solubility of I while at high concentrations solubility was enhanced. X-Ray and infrared analysis of the systems suggested the presence of an amorphous form of I in coprecipitate systems. The dissolution data were consistent with a physical model which takes account of the roles played by crystalline and amorphous I together with the complexing and crystal growth inhibiting effect of II on I.[22]

Huang and Niazi studied a fast dissolving polymorphic form of mercaptopurine (I) which can be useful in increasing bioavailability.

Differential thermal X-ray diffraction analyses showed 2 polymorphic forms of I which when tested for solubility, showed identical results. However dis-

solution rates for the high energy polymorph were twice those of the lower energy form.[24]

Kohler et al showed that the two polymorphic modifications of 2-sulfanilamido 5-(β-hydroxy ethoxy) pyrimidine were characterized by their different crystal shapes, melting points, IR spectra, and dissolution profiles. In contact with water one polymorph was partialy or completely able to transform into the other form, however it was not possible to quantity this transition.[24]

Differential scanning calorimietry and hot stage microscopy were used by Ford and Rubinstein to obtain phase diagrams of the binary system of indomethacin (I) and polyethlene glycol 6000 (II). The solubility of I in II solutions and the dissolution rate profiles of I and II compressed and melt disks were determined. Results showed that II increased the solubility and dissolution rate of I, an optimum being obtained from the 15% I and 85% II system. The melts exhibited higher dissolution rates than the compressed disks.[25]

Dilute, saturated and supersaturated solutions of cholorothiazide (I) and Polyvinyl Pyrrolidone (Povidone II) coprecipitates and mechanical mixes were prepared and evaluated for permeability through an everted rat intestine by O Driscoll, and Corrigan

Dissolution profiles showed that relative to pure I, coprecipitation enhanced dissolution by a factor of 18.9 and mechanical mixes caused 2.84 fold increase. Reduced permeability from dilute solutions containing II and enhanced dissolution from a mechanical mixture were explained by the formation of a soluble complex. Transport rates from a supersaturated solution were also enhanced in the presence of II.

It was concluded that high dose to solubility ratios were responsible for lack of I transport and that enhanced transport in the presence of II was due to inhibition of I crystallisation.[26]

Merkle prepared by the solvent method coprecipitates containing hydrocortisone (I) or prednisolone (II) and polyvinyl pyrrolidones (Povidone PVP) ranging in molecular weight between 11500 and 10000, and a physiochemical evaluation of the resultant products was undertaken.

Enhanced drug release rates were found only up to a limit of 20% for I and 4% for II. Higher drug fractions led to amorphous or crystalline formations covering the dissolution, surface and severe inhibition of polyme dissolution. Fast drug release was found to be restricted to the low molecular weight polymer formulations. Factors influencing drug release rates in this range were dissolution rate of the polymer and the ratio of drug to polymer weight fractions.[27]

Then Dommeyer et al studied the factors affecting the physiochemical properties of tolbutamide (I) during coprecipitation with polyvinyl pyrrolidone (Povidone).

In ethanolic solutions, I properties varied according to the concentration of the hydrophilic vehicle, cording to the concentration of the hydrophilic vehicle, as well as by direct effects of the solvent. Therefore dif erent crystalline states and one amorphous state of I were found during coprecipitation. Particle size was found to play the most important role in coprecipitation dissolution.[28]

By dissolution rate testing Tuladhar et al evaluated the relative particle size changes for phenylbutazone (I) during compression and crushing and bonding mechanisms associated with the changes.

The effects of polymorphism, compression pressure, drug content and the rate of compression were also studied. Crushing and bonding mechanisms in high concentration of drug were dependent on the original particle size and the polymorphic form of I. With low concentrations diluents protected I particles from bonding. The effects of different types of diluents were also discussed. Decreasing the rate of compression

decreassed the amount of particle bonding with smaller particles, but larger particles were independent of the compression rates.[29]

Later Tuladhar, and Carless studied the preparation and thermal characterication of 5 phanyl butazone using differential scanning calorimetery, in an aqueous buffer of pH 7.5. Rapid heating rates produced single endothermic peaks due to melting, but slower heating rates resulted in interconversion of 3 polymorphs to the more stable form. Interconversion on grinding the polymorphs was also observed Equilibrium solubility and intrinsic dissolution rates showed that the dissolution process could be described by a Berthoud model. The effect of some tablet excipients on the dissolution processes was also shown.[30]

C. Absorption

Yama moto et al prepared ground mixtures of chloramphenicol palmitate (I) and Micro-crystalline Cellulose using Form A (stable form) and form B (metastable form) of I.

Dissolution and enzymatic hydrolysis rates of the ground mixture were greater than that of Form A. The enzymatic hydrolysis rate of Form B was as fast as that of the ground mixture even when its dissolution rate was not much greater than that of Form A. Four preparations, Form A, Form B, Form A ground mixture, and Form B ground mixture were administered in a random crossover fashion to 5 human subjects and urinary metabolite excretion data were evaluated for drug absorption. After oral administration of the ground mixtures the drug was found to be more uniformly absorbed. A 20 fold increase in absorption was also observed by grinding form A.[31]

Absorption of indomethacin (I) from the rabbit rectum was examined in suppositories containing I polymorphs (α or γ forms) by Yokoyam et al. Rectal suppositories were made with Witespsol H-12. Plasma levels of the 2 α form of I were higher than those of γ form. The commercial product made with polyethylene glycol base was also examined. The plasma levels of I in polyethylene glycol base were similar to those of α form.

The relationship between the thermodynamic activities of I polymorphs and their rectal absorption was also discussed.[32]

D. Bioavailability

The bioavailability of two crystal forms of sulfameter was determined by Khalafallah, and Khalil from the urinary excretion data of two female and six male volunteers.

One gram of either crystal form was suspended in a mixture previously shown to inhibit polymorphic transformation and immediately administered after an overnight fast period. A crossover study was performed with the same volunteers after one month. Although the urine data revealed a significant difference in the rate of absorption of the two forms, no significant difference was observed in the extent of absorption of both forms as indicated by the 72 hour urinary excretion data. It was suggested that crystal forms of sulfameter may be compared as to their bioavailability by comparing their excretion rate during the absorption phase. Urinary excretion data are also suggested as a simple alternative to blood level data in studying the kinetics of absorption and deriving absorption parameters that enable the comparison of different formulations of sulfameter.[33]

The determination of the transition temperature and heat of transition between three polymorphic forms of phenobarbittal (I) form 1, form 2, and the hydrate was reported by Kato and Watanabe.

Also the bioavailability of these 3 forms were evaluated by the in vivo absorption test after oral administration to rabbits.

The transition temperature and the heat of transition between form 1, and form 2 and between the hydrate and form 2 were determined to be 80.9 and 0.23 kcal/mole. and 49.1 and 1.52 kcal/mole by the solubility measurement. These values were in agreement with those obtained by other methods. The crystalline energy differences were in agreement with those of the heat of transition by the solubility measurement. In the in vivo absorption test the plasma concentration versus time curves of the 3 forms I in rabbits indicated that each form was similar and these polymorphic states do not effect bioavailability.[24]

Dragnet :- Brughmans and Bouche, investigated polymorphism in 11 samples of pentobarbital using differential scanning calorimetry, thermomicroscopy, IR spectrophotometry, and X-ray diffraction.

The conformity of the samples to European Pharmacopoeia specifications was also studied. The existence of 2 polymorphs was reported in some of the samples. Other samples were mixtures of polymorphs or were pure polymorphs. The different forms had different, solubilities, dissolution rates and bioavailabilities[25].

Camerom et al studied the solvation of chloremphemiol stegrate and chloramphenicol palmitate and various analytical techniques were used to characterize the resulting solvates.

Metastable polymorphic forms of chloramphenicol were formed, however the high crystallinity and low enzymatic hydrolysis rate constants determined in vitro suggested low potential availability.[26]

E. Bioequivalence

Physiochemical characteristics of chloramphenicol palmitate form B, prepared by different methods, were quantified and related to drug bioavailability by Bernobei et al.

The dimensions and morphology of particles, thermo microscopic characteristics, IR spectra, X-ray diffraction results, degree of crystallinity, and the velocity constant of enzymatic hydrolysis in vitro were obtained.

An inverse relationship was found between relative crystallinity and in vitro enzymatic, hydrolysis, suggesting an inverse relationship with bioavailability. Pharmacopoeial tests to standardize the degree of crystallization for chloramphenicol are recommended.[27]

F. Toxicity

Ghielmetti, and Bruzzese found marked differences in LD 50 values between various batches of polyene antibiotics (meparticin and nystatin) after IP administration in suspension to mice. Such differences do not seem attributable to the particle size but to different crystal structures of the products, which modify their solubility and biological availability. In the samples obtained by chemical treatments of some batches of the polyene substances, it has been possible to change the toxicity drastically and then to bring it back to its original value.[28]

III. Manufacturing

Various crystal forms of sulfathiazole, barbital and aspirin were compressed in a single punch tablet machine instrumented to monitor axially applied and radially transmitted forces, and upper punch movement. The effects of this were studied by Summers, Enever, and Carless.

The changes in radial stress during the compression cycle depended upon the polymorphic forms of the compressed material. The results were rationalized in terms of the degree of plastic flow/crushing that occurred with each material, and the degree to which the final compact underwent elastic compression.[29]

A method was described for the preparation of sterile hydrocortisone as the stable polymorph A by evaporation from a mixture of methanol and ethanol by Chrai et al. This procedure can be adopted to large scale manufacture.[40]

Data was collected by Ibrahim from X-ray diffraction, thermal analysis, IR spectroscopy, and solubility studies and were used for identification and characterization of 4 crystalline modifications of phenylbutazone.

The thermal behaviour of the polymorphs under different treatment conditions was also investigated. Compression of the thermodynamically unstable forms, at a compression force of 1590-2040 kg. induced polymorphic changes in the crystals. Similar changes were also produced through grinding. The apparent equilibrium solubilities were determined as was the dissolution as compressed disks in an equeous medium. The small effective surface area possessed by one polymorph resulted in slow dissolution.[41]

Studies on the crystal transformation of methisazone (I) upon grinding was made by Lee and Hersey by X-ray diffraction, IR spectra and differential thermal analysis carried out on freshly ground, unground and micronised I. All these materials give distinctive diffraction patterns indicating the presence of at least 2 polymorphs. There polymorphic changes may explain the increased solubility, biological activity and stability obtained with the use of micronized (I) in pharmaceutical formulations.[42]

Junginger studied the effects of grinding on the various polymorphs of sulfanilamide (I). Grinding of polymorph (I) in a colloid mill produces a 95% phase transformation into polymorph II. On the other hand, when polymorph II is ground under identical conditions, the same phase equilibrium is reached as on grinding phase I. Investigations on the nucleation phase of this phase transformation prove that up to a degree of phase transformation of 50% the Prout Tompkins mechanism is performed. Milling polymorph III under the same conditions produces a quantitative phase transformation into polymorph II. A more extensive grinding leads to the same phase equilibrium consisting of 95% polymorph II and 5% polymorph I. On grinding polymorph III, the nucleation phase of polymorph II is superposed by the milling process, so that Prout-Tompkins mechanism cannot be fulfilled.

The phase transformations were proved by X-ray crystallography (goniometer methods) and by measuring the solution enthalpies of the ground products. In addition, the increase of temperature during the milling process was determined. The temperature increases faster when the milling process is repeated because the need of energy to get smaller particles is lower than for the first milling process.[43]

Florence used infrared spectroscopy, X-ray diffractometry, differential thermal analysis, scanning electron microscoppy, solubility and dissolution rate measurements to demonstrate that pulverization of digoxin (I) crystals resulted in the appearance of an amorphous phase. The study of spironolactone and 17-β estradiol also showed that these compounds undergo changes in their crystallinitiy on grinding. Since the dissolution characteristics of poorly soluble drugs may be complex functions of surface area and crystallinity it was concluded that the most pertinent method for standardizing a sample of a polymorph drug of low solubility is by means of a powder dissolution test.[44]

Conte et al compared the compression properties of 2 polymorphic forms of sulfamethoxydiazine (sulfameter I). Tablets obtained with I crystalline form has better particle size distribution, disintegration time, porosity, and friability, than, the other I polymorphic form. The best formulations were obtained when potato starch and lactose were used as diluents.[45]

The conditions for preparing 2 known crystalline polymorphs of trimethoprim (I) of a new crystalline form and of I monohydrate were studied by Bettin-

atti et al. The crystals were characterized by IR spectroscopy, thermal and thermogravimetric analysis, and by x-ray diffractometry.[46]

The effects of wet granulation, excipients and compression on polymorphic changes in sulfanilamide were studied by Gruaud et al.[47]

The crystal changes during tablet compression were studied by Fuhrer and the compression characteristics of polymorphic compounds were also noted.[48]

IV. Microencapsulation

Takenaka and Kawashima[49] investigated the effects of cellulose acetate phthalate and excipients such as talc colloidal silica and montmorillonite on the polymorphism of sulfamethoxazole in microcapsules.

The surface topography varied with the type of excipient and the pH of the suspending medium. Polymorphic transformations of sulfamethoxazole were attributed to interactions with cellulose acetate phthalate. Talc was the only excipient to contribute to sulfamethoxazole polymorphism.[49]

Various microscapsule formulations of sulfamethoxazole containing either xanthan gum or guargum and colloidal silicon dioxide or cellulose acetate phthalate were evaluated for release behaviour, physicochemical characteristics and drug polymorphism by Kawashima et al. Silica preparations produced increased particle size and improved physical characteristics. Crystalline forms I, II and III of sulfamethoxazole were observed in formulations containing cellulose acetate phthalate. Colloidal silica products showed only form I crystals. Formulations obtained from aqueous solutions had prolonged drug release rates from tablets, while those obtained from ammonium hydroxide exhibited rapid drug releases.[50]

V. ANTIGEN FORMATION :

Using a reversed phase high pressure liquid chromatographic method an investigation of the time courses of formation of ampicillin di and polymers in aqueous solutions of ampicillin sodium (I) at different initial concentrations (1 to 20%, w/v) was carried out and studied by Larsen and Bundgaard. In 10 to 20% solutions at room temperature, di, tetra and hexamers account for more than 90% of the products formed by I total degradation. In 1 to 5% solutions the dimer and α amino penicilloic acids constituted the major degradation products. For each individual polymer, ranging in size from the dimer to the octamer quantitative data for the amounts formed during storage of I solutions under practical clinical conditions were calculated, and the influence of storage time of the I solutions on their antigenic activity was discussed.[51]

VI. OINTMENTS

Borka studied the problems of polymorphism in pharmaceutical preparations and emphasized more on the risk of crystal growth in eye ointments due to unstable polymorph conditions.[52]

In order to characterize the crystalline state of hydrophilic ointment (I) as well as of its components, X-ray studies (using Klessing's low angle technique and goniometric diffractometry) were carried out and studied by Fuhrer et al.

Both cetyl and stearyl alcohols crystallize in a mixture of β_0 and γ [4] Polymorphs. Depending on the conditions of crystallization one or the other polymorphic phase is in excess. The mixture of these two alcohols, contostearyl alcohol forms mixed crystals with a uniform Bragg's distance, which is between the 2 β_0 polymorphic forms of the single components. On the other hand sodium cetyl sulphate (II) and sodium stearyl sulphate (III) crystallize as seperate entities from their mixtures.

The predominant species in emulsifying wax (90% cetostearyl alcohol and 10% II and III) are mixed crystals which consist mainly of cetyl alcohol, and II and partly of stearyl alcohol. In addition, mixed crystals of stearyl alcohol and III are found in small amounts. In I both types of mixed crystals from a framework of gel in which white soft paraffin and the liquid components of the white petrolatum are immobilized either mechanically or by capillary attraction. Since the wide angle interferences are nearly identical, it may be assumed that the paraffinic carbon chains of all components of the ointment can form similar orthorhombic subcells.[53]

The influence of ointment composition and storage temperature on the conversion of anhydrous prednisolone (I) to its hydrated form in oil in water type cintments was studied using an x-ray diffractometer and a polaring microscope by Kacho et al.

When stearyl alcohol or cetyl alcohol alone was added to the ointment anhydrous I was converted into the hydrate at a low temperature (5°). However, when a mixture of alcohols was used in a proper ratio, the conversion of the anhydrous to the hydrated form was retarded. When stearyl alcohol and cetylalcohol were mixed in the ratio of approx. 2 : 3, the anhydrous form remained most stable. When the ointment was stored at a high temperature (37°) for a long time and then moved to a low temperature (5°) for storage, conversion to the hydrate was difficult. These results were due to the 3 polymorphisims (α r, and β) of long chain alcohols. The ointment structure containing the α form was stable enough to stabilize anhydrous I while that containing the β or r form was less stable.[54]

VII. Suppositories

Nurnberg, Schenk, and Kohr, studied the methods of production, composition and melting behaviour of adeps solidus and the conditions under which polymorphic modifications result were shown experimentally with the aid of differential scanning colorimetry. Thermograms of 7 different suppository bases were illustrated and comparisons between them were made.[55]

Luversidge, & Grant, showed that in order to determine the most suitable compositions for suppository bases from the point of view of melting point, and polymorphic change, complete phase diagrams of binary mixtures of some monoacid triglycerides, namely tricaprin (glyceryl-tri-n-decanoate, Dynasan 110, I), trilaurin (glyceryl-tri-n-di decanoate, Dynasan 112, II), trimyristin (glyceryl, tri-n-hexa tetradecanoate, Dynasan 114, III), tripalmitin (glyceryl tri-n-hexa decanoate, Dynasan 116, IV) and tristearin (glyceryl tri-n-octa dercenoate, glyceryl tristearate, dynasan tri-n-octa decanoate, glyceryl tristearate, dynasen 118, V). Witepsol W 35, Witepsol E 75 and Suppocire A, were derived, using differential thermal analysis as a heating method.

The increase in melting point on storage was found to be closely associated with the conversion of the α and β' polymorphs of the constitutent bases to the more stable β polymorph. The rate of this process was found to decrease with increasing chain length. Tricaprin II, III, IV and V showed eutectic or monotectic behaviour, the eutectic composition of one varying by about 20% from the others next to it, with respect to the higher melting components.

From the results, 2-8% V in I, 3-10% IV in I, 10-25% III in I, 55-65% II in I and 40% II in I (all W/W) were proposed as suppository bases.[56]

Thoma performed an in vitro study of the physical stability of 107 commercial hard fat (Adeps solidus) suppository preparations, comparing the effects of storage conditions on the melting times is presented.

The techniques used included the Erweka Penetration Tester PM 3, the Selnikar — Fantelli method, the suppository melting Tester SSP and the apparatus of the European Pharmacopoeia II.

The observed melting times showed a considerable dependency on the age of the preparations. The changes were due to the polymorphic behaviour of the semi-synthetic triglyceride suppository bases. Subject to the temperature, hard fat crystallizes in an α or β modification and changes to β polymorph within months or years. All bases showed this phase transition as a function of storage temperature.[37]

The influence of the liquid phase on the A and B transition of semisynthetic fatty suppository bases, including Witepsol H-15 and E-75 (trilaurin) during storage was studied by Yosheno et al.

The case where the liquid phase was produced only from the molten vehicle containing no liquid additive was also examined. The activation energy of transition was compared in the presence and absence of liquid additives. The transition mechanism was considered to involve dissolution of the solid A form in the intervening liquid phase followed by crystallization as solid B form.[38]

The polymorphism of hard fat (Adeps solidus) in suppository bases was demonstrated by X-ray diffraction and studied by Thoma, Serno & Precht. Temperature and storage effects on polymorphism were discussed. Differences between several types of base were found to be due to different chain lengths of the triglycerides[39]

Differential thermal analysis was used to demonstrate the 2 polymorphic crystal forms of hard fat (Adeps solidus) suppository bases resulting from solidification of a molten mass, dependent on temperature by Thoma.

Transition from one polymorphic form to the other during storage and effects of the transition on suppository hardening were discussed. Addition of soy lecithin was shown to alter crystal behaviour and stabilize the suppositories.[40]

VII. Stability

Various analytical techniques were used to investigate the physical characteristics of sulfa-methoxazole (I) instability in aqueous suspensions of Graf. Transformation of I to a semihydrate form was found to be the major characteristic to I instability formulation methods for inhibiting this transformation were studied. Methyl cellulose, povidone and sucrose used as suspension additives inhibited the transformation while carmellose sodium (carboxy methyl cellulose sodium) enhanced this effect[41]

IX. Effect of Ageing

The effect of ageing on the disolution of indomethacin (I) solid dispersions in polyethylene glycol 6000 (II) was studied by Ford and Rubinstein using constant surface area disks stored at various temperatures. It was determined that ageing markedly reduces dissolution rates. The changes were complex and dependent upon disk concentrations and storage conditions. Melts stored at 4°C containing 5 or 10% I showed slow decreases in dissolution rates which still decreased even after one year storage. However, melts containing 25% I stored at 35°C exhibited large dissolution rate decreases initially which then remained relatively constant after 10 days storage.

The presence of moisture also played a major role in reducing dissolution rates. Photomicroscopy revealed changes in structure of the melts dependent on concentration which were thought to produce the dissolution rate changes.[42]

X. Forensic Aspects

The forensic aspects of heroin (diacetyl morphine) were examined by Borka in its existence as a polymorph. A form with a slightly lower melting point and an irregular IR Spectroscopy was found. These irregularities donot necessarily indicate impure I, but may be explained by polymorphism.[43]

It may thus be concluded that polymorphism is one of the most important property of drug compounds which might affect various formulation parameters and performance characterestics of dosage forms. It would therefore be desirable that polymorphic behaviour of drug alone and in presence of formulation additives is studied thoroughly.

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